Management of aneurysmal subarachnoid hemorrhage patients with antiplatelet use before the initial hemorrhage: an international survey

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Abstract: INTRODUCTION The case fatality in aneurysmal subarachnoid hemorrhage (aSAH) is 50% due to the initial hemorrhage or subsequent complications like aneurysmal rebleed or delayed cerebral ischemia (DCI). One factor that might influence the initial brain damage or subsequent complications is the use of antiplatelet medication before the initial hemorrhage. The goal of this survey was to assess the different management options of patients with aSAH with antiplatelet use before the initial hemorrhage. MATERIAL AND METHODS An anonymous survey of 11 multiple-choice questions about management of aSAH patients with antiplatelet use before the initial hemorrhage was distributed to the international panel of attendees of the European Association of Neurosurgical Societies (EANS) annual meeting in Venice, Italy at 1-5 October 2017. RESULTS A total of 258 (54%) completed surveys were returned. In about 80%, the departments of neurosurgery and neurology were responsible for acute management of aSAH patients, whereas in 15% the intensive care unit. Department guidelines were present in 32%. In 65%, the responders always stop the antiplatelet agent at admission and in 4.3% are thrombocytes always transfused. When a guideline is present, the neurospecialists consider thrombocyte transfusion more often (83% vs. 65% p=0.02). CONCLUSION Our survey among mainly European neurosurgeons show that there is a significant variability in the management of aSAH patients who have been using antiplatelets before the initial hemorrhage. These findings emphasize the importance of the development of evidence-based guidelines for management of patients with aSAH and antiplatelet use before the initial hemorrhage.

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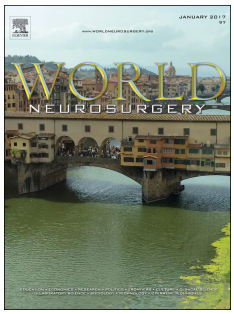

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Management of aneurysmal subarachnoid hemorrhage patients with antiplatelet use before the initial hemorrhage: an international survey

Cover Title: Management of antiplatelet use in aneurysmal subarachnoid hemorrhage: survey

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Abstract

Introduction The case fatality in aneurysmal subarachnoid hemorrhage (aSAH) is 50% due to the initial hemorrhage or subsequent complications like aneurysmal rebleed or delayed cerebral ischemia (DCI). One factor that might influence the initial brain damage or subsequent complications is the use of antiplatelet medication before the initial hemorrhage. The goal of this survey was to assess the different management options of patients with aSAH with antiplatelet use before the initial hemorrhage.

Material and methods An anonymous survey of 11 multiple-choice questions about management of aSAH patients with antiplatelet use before the initial hemorrhage was distributed to the international panel of attendees of the European Association of Neurosurgical Societies (EANS) annual meeting in Venice, Italy at 1-5 October 2017.

Results A total of 258 (54%) completed surveys were returned. In about 80%, the departments of neurosurgery and neurology were responsible for acute management of aSAH patients, whereas in 15% the intensive care unit. Department guidelines were present in 32%. In 65%, the responders always stop the antiplatelet agent at admission and in 4.3% are thrombocytes always transfused. When a guideline is present, the neurospecialists consider thrombocyte transfusion more often (83% vs. 65% p=0.02).

Conclusion Our survey among mainly European neurosurgeons show that there is a significant variability in the management of aSAH patients who have been using antiplatelets before the initial hemorrhage. These findings emphasize the importance of the development of evidence-based guidelines for management of patients with aSAH and antiplatelet use before the initial hemorrhage.

1 Introduction

In patients with aneurysmal subarachnoid hemorrhage (aSAH), many factors are known to influence initial hemorrhage severity, rebleed rate and delayed cerebral ischemia (DCI) (e.g. age, aneurysm size, history of hypertension, heavy alcohol consumption, cigarette smoking). Many of those factors have been investigated and assessed whether they improve functional outcome. (1) Unfortunately the results are disappointing and it seems that the complications are multifactorial. One factor that might influence the initial hemorrhage severity, rebleed rate and rate of DCI, is the use of antiplatelet agents before the initial hemorrhage.

In patients younger than 60 the prehemorrhage use of antiplatelet agents does probably not increase the risk of poor outcome. (2) When antiplatelet agents are administered after the initial SAH, a trend towards better outcome was seen in a Cochrane review. (3) A large multicenter trial with early thrombocyte transfusion, however, could not confirm an improvement in poor outcome. (4) Although antiplatelet use probably increases the risk of rebleeds (3, 5), which might be reduced by acute thrombocyte transfusion, the risks of thrombocyte transfusion after aSAH has not been investigated. Results of the recent PATCH study (6), in which aSAH patients were excluded showed that patients with intracerebral hemorrhages have a higher case fatality rate after acute thrombocyte transfusion in patients with prehemorrhage antiplatelet agents use. This finding opened the discussion whether thrombocyte transfusion could be harmful to aSAH patients instead of beneficial.

The topic regarding stopping antiplatelet agents and whether to transfuse thrombocytes in aSAH patients remains an issue of debate. We therefore developed a survey to assess how neurospecialists deal with aSAH patients who use antiplatelet agents before the initial hemorrhage.

2 Material and methods

Survey development and distribution

We developed an anonymous survey containing 11 multiple-choice questions (Figure 1) regarding management of aSAH patients who use antiplatelet agents before the initial hemorrhage. We included more general questions about specialist and the institution type: country, specialty, number of aSAH patients per year, treatment-leading department at the admission of the patient. Furthermore, we asked about the existence of a guideline for treating patients with aSAH who have been using antiplatelet agents before the initial hemorrhage and which treating specialist makes the decision to transfuse thrombocytes. Questions about stopping the antiplatelet agents and transfusion of thrombocytes, including clinical status of patients have also been asked.

A paper version of this survey was distributed to the attendees of the annual meeting of the European Association of Neurosurgical Societies (EANS), which took place in Venice, Italy at 1-5 October 2017 and collected immediately after completing the survey.

Data analysis

Data were manually imported in a digital database (Statistical Package for the Social Science (SPSS) version 24 for Windows (IBM, Armonk, New York, USA). To simplify the comparison between answer options, we combined questions that were not answered with "always" or "never", into a group called "individualized decision". The various results were reported as value or proportion (%). Descriptive statistics were used to analyze the collected data. Categorical data were analyzed using the chi-square test. Statistical significance was defined at $p < 0.05$.

3 Results

A total of 478 surveys were distributed, and 258 (54%) completed surveys were returned. The responders were distributed among 51 different countries, with the majority originating from Europe. Figure 2A shows the continental geographical distribution of responders whereas figure 2B shows the distribution of completed surveys among European countries. The baseline characteristics of 258 respondents to the survey are shown in Table 1.

About half of the responders worked in hospitals where more than 50 aSAH patients were treated per year. The departments of neurosurgery and neurology were responsible for primary management of aSAH in about 80%, whereas in 15% the intensive care unit took care of it. Department guidelines regarding management of antiplatelet agents use in aSAH patients were present in 32%. No difference in the presence of a guideline was found between Western and Eastern Europe (32% versus 33%, respectively). Similarly, 30% of Asian clinicians and 35% of clinicians from other countries had hospital guidelines. Approximately two-thirds (65%) of all responders always stop the administration of antiplatelet agents at admission and 4.3 % always transfuse thrombocytes (Table 2).

The rate of decision to stop the antiplatelet agent and/or transfuse thrombocytes was different between hospitals who had a guideline or not. Table 3 shows the crosstab with distribution of answers. Neurospecialists tend to stop antiplatelet agents more often in institutions who use guidelines ($p = 0.06$), whereas they transfuse thrombocytes significantly more often $p = 0.02$). Stopping the antiplatelet agents and acute transfusion of thrombocytes are based on an individualized decision in 39% and 79%, respectively.

4 Discussion

This international survey, distributed at EANS Congress in Venice in October 2017, offers insights into the current practice of management of patients who use antiplatelet agents before aSAH. The majority (82%) of the responders were originating from Europe and 18% from non-European countries (Table 1). The results show that there is a large difference in management among institutions. This emphasizes the lack of evidence-based guidelines for managing antiplatelet agents and thrombocyte transfusion in aSAH patients.

1.1 Importance of guidelines in clinical practice

About one third (32.2%) of clinicians work in institutions in which guidelines are present for management of aSAH patients with antiplatelet use before the initial hemorrhage. No difference in geographical distribution regarding department guidelines was found. This confirms our suspicion that a lack of in-hospital guidelines is a general phenomenon. Furthermore, a lack of guidelines and agreement could lead to different management at the same department by different clinicians. The American Heart Association/American Stroke Association has published general guidelines for the management of aSAH. These guidelines offer a framework for treatment of aSAH patients and improve their outcome. (7) Remarkably, analyses of Gritti et al. (8) showed that written protocols for aSAH management were not consistently used across institutions. Our analysis showed an interesting phenomenon regarding stopping the antiplatelet agents and acute transfusion of thrombocytes. Namely, antiplatelet agents tend to be stopped more often if institutional guidelines are present and thrombocytes are transfused in acute phase after aSAH significantly more often. These findings suggest that guidelines help in clinical decision-making regarding rare but relevant situations. Nevertheless, the clinical impact of stopping antiplatelet agents or

transfusion of thrombocytes is still unclear because literature on outcome after aSAH with the prehemorrhage use of antiplatelet agents is scare and show conflicting results.

4.2 Prehemorrhage use of antiplatelets

Administration of antiplatelet agents after aSAH is not recommended according to the current literature. (3, 7, 9) However, there is no literature known that describe how to deal with patients who already used antiplatelet agents before the initial hemorrhage. The influence of use of antiplatelet agents before initial hemorrhage was reported by Kato et al.(2) who reported that antiplatelet use significantly improved prognosis, albeit only in patients younger than 60 years. Gross et al. (10) suggested a potential beneficial effect of aspirin in the setting of aSAH by weighing the risk of aneurysm rupture against its potential adverse effects on hemorrhage severity. Additionally, Konczalla et al. (11) concluded that use of antithrombotic medication was associated with a significantly worse outcome and a higher mortality rate after aneurysmal and non-aneurysmal SAH.

4.3 Thrombocyte transfusion in intracerebral hemorrhage

No studies are known that evaluated the safety and efficacy of thrombocyte transfusion in patients with aSAH. Some reasons to transfuse thrombocytes after aSAH in patients who use of antiplatelet agents before the initial hemorrhage might be a possible reduction of rebleeds, less intracerebral hemorrhage after insertion of external ventricular drain or less risk for diffuse bleeding and postoperative hemorrhage by microsurgical clipping. (3, 5) Thrombocyte transfusion may be associated with activation of an inflammatory response and therefore potential harmful effect on DCI, and effects of the increased production of cytokines associated with the thrombocyte transfusion.

Thrombocyte transfusion in patients with spontaneous intracerebral hemorrhage (ICH), however, has been studied. (12-15) Recently, the results of the randomized controlled PATCH trial, comparing thrombocyte transfusion versus standard care without thrombocyte transfusion, were published. (6) The results show that patients with spontaneous ICH had a higher case fatality rate when thrombocytes were acutely transfused. This study emphasized the harmful effect of thrombocyte transfusion in patient with spontaneous ICH. Although patients with aSAH were not included in the study it opened the discussion whether thrombocyte transfusion in aSAH could be harmful to patients instead of beneficial. Based on the current knowledge, however, no recommendation regarding thrombocyte transfusion can be given in patients with aSAH.

As the current literature fails guidelines regarding acute thrombocyte transfusion in patients with antiplatelet use before the aSAH, it is not surprising that 79% of respondents to our survey make an individualized decision. Antiplatelet type, result of aggregation test, kind of treatment (surgical or endovascular) as well as presence of intracerebral and/or intraventricular hemorrhage appear to have an impact on the decision to transfuse or not.

Transfusion of thrombocytes in acute phase after aSAH is decided interdisciplinary in 42%. This supports the importance of interdisciplinary guidelines among specialists who treat aSAH patients in order to achieve the best treatment based on current available literature and individual experiences. In approximately one fourth (26%) the neurosurgeon decides to transfuse thrombocytes which is probably a result of the importance of optimal intraoperative coagulation. In the majority of cases the amount of thrombocyte transfusion depends on type of antiplatelet agent which again emphasizes the personalized and individualized treatment of these patients.

4.4 Dilemmas in surgical and interventional procedures

The lack of evidence and guidelines for management of pre-event and pre-surgical use of antiplatelet agents is not just a neurosurgical dilemma - other disciplines have similar problems. The current literature is contradictory regarding the question whether to continue or discontinue antiplatelet agents in the perioperative period. The beneficial effect of antiplatelet agents, however, is well documented in secondary prevention of myocardial infarction or stroke in patients with ischemic heart and cerebrovascular disease. (16) Despite evidence of benefit in these patients, antiplatelet agents are often discontinued before surgery due to the risk of perioperative bleeding. (17) However, some recent publications recommend that aspirin should not be routinely stopped in the perioperative period in cardiac surgery and spinal surgery patients. (18-21)

Intracranial surgery, in comparison to other non-cranial surgeries, is associated more often with severe complications due to postoperative hemorrhages and therefore coagulation need to be optimal. Interestingly, in patients undergoing craniotomy for a brain tumor perioperative low dose aspirin use was not associated with an increased risk of bleeding complications or need for surgical revision. (22) One study (23) showed that aspirin administration in patients with increased risk for endovascular complications significantly decreased the rate of periprocedural thromboembolic events. The rate of intracranial hemorrhages was not increased. On the contrary, another recent study (24) investigated whether the benefit of endovascular treatment compared to neurosurgical clipping is influenced by use of antiplatelet agents after coiling. The results of this study do not support the assumption that antiplatelets during or after endovascular coiling improve outcome in patients with SAH.

Lastly, it is important to be aware of the possible (extracranial) complications (e.g. ischemic heart infarct, re-stenosis of coronary stents or bypasses pulmonary embolism) after stopping

antiplatelet agents. Ischemic strokes and myocardial infarctions were seen more than twice as much as recurrent ICH over a median of 41 months in a large cohort study. (25) Additionally, a study performed in 13 German stroke centers found no increase in recurrent ICH using antiplatelet agents versus no antithrombotic medication. (26) These data emphasize the importance of considering not only the intracranial but also the cardiac risks to decide whether to stop antiplatelet agents.

4.1 Limitations

Our survey has several limitations, particularly with regard to responder bias and generalizability. First, the survey was distributed to participants of the EANS congress in Venice and therefore the results more or less show the current European practice and might not be generalized globally because of the small number of responders from non-European countries. Second, responses were voluntary and could lead to a selection bias for people with a particular interest and/or knowledge in these issues. Furthermore, some limitations are due to the survey design: the working institution and training level (resident vs. attending) of respondents were not asked.

5 Conclusion

Our survey showthat there is a significant variability in management of aSAH patients who use antiplatelet agents before the initial hemorrhage. The presence of an in-hospital guideline appears to influence the decision of stopping the antiplatelet agents or to transfuse thrombocytes. Current literature is inconclusive regarding management of patients who use

antiplatelet agents before aSAH and therefore optimal management is unclear. These findings emphasize the importance of the development of evidence-based guidelines and the need for randomized clinical trials in patients with aSAH and use of antiplatelet agents before the initial hemorrhage.

Authors' contributions

Dr. Sebök: Study concept and design. Acquisition of data. Analysis and interpretation. Constructed the manuscript.

Prof. Keller: Study concept and design. Analysis and interpretation. Critical revision of the manuscript for important intellectual content.

Dr. van Niftrik: Acquisition of data.

Prof. Regli: Study concept and design. Critical revision of the manuscript for important intellectual content. Study supervision.

Dr. Germans: Study concept and design. Acquisition of data. Analysis and interpretation. Study supervision. Critical revision of the manuscript for important intellectual content.

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Figure caption:

Figure 1: Survey questions

Figure 2: A.Distribution of completed surveys among continents. B. Distribution of numbers of completed surveys among European countries.

Tables

Table 1 Baseline characteristics of 258 respondents to the survey

Table 2 Results of survey

Table 3. Crosstab of stop of antiplatelet agents and thrombocyte transfusion data in comparison to in-hospital guideline

Tables

Table 1 Baseline characteristics of 258 respondents to the survey

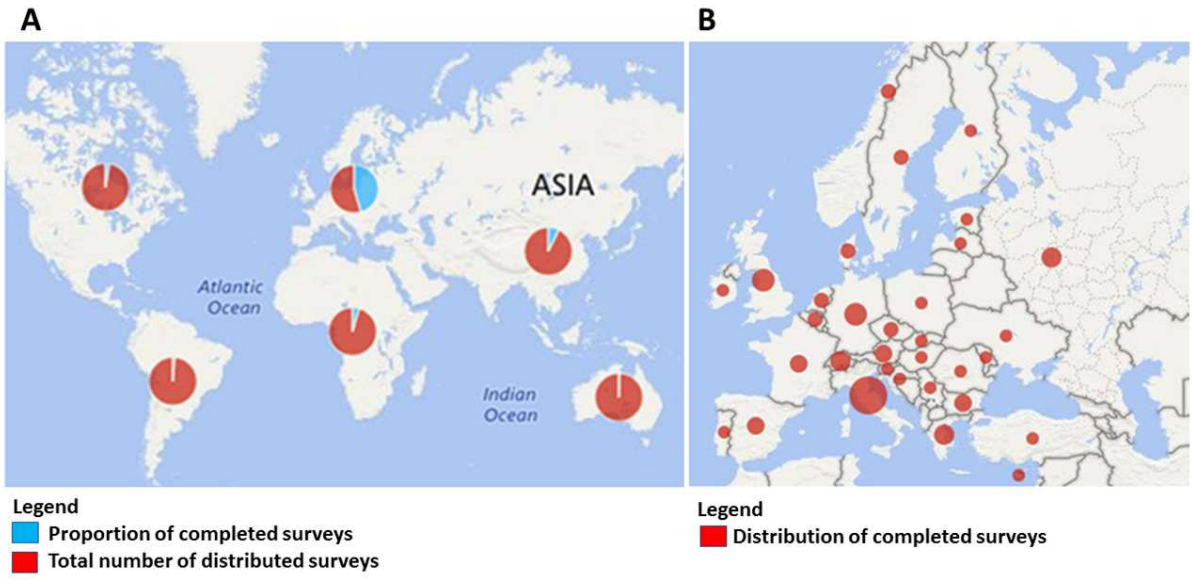
	Number of respondents (%)
Continent	
Western Europe*	151 (58.5)
Eastern Europe*	60 (23.3)
Asia	24 (9.3)
Other	23 (8.9)
Speciality	
Neurosurgery	254 (98.4)
Other	4 (1.6)
Number of aSAH treated in the hospital per year	
<25	40 (15.5)
25-50	87 (33.7)
50-100	84 (32.6)
>100	47 (18.2)
Department which is primary responsible for aSAH treatment	
Neurosurgery	184 (71.3)
Neurology	21 (8.1)
Intensive care	38 (14.7)
Other	15 (5.9)
Guidelines for treating patients with aSAH who have been using antiplatelet agents before onset of hemorrhage	
Yes	83 (32.2)
No	175 (67.8)
***Boarder between countries of Western and Eastern Europe was chosen according to historical and political statement. (31) Scandinavian countries belong to Western Europe, Baltic countries to Eastern Europe. Russia and Turkey as Euro-Asian countries were added to Eastern Europe.**	

Table 2 Results of survey

	Number of respondents (%)
Stopping administration of platelet agents	
Never	9 (3.5)
Always	167 (64.7)
individualized decision	**82 (31.8)**
depends on antiplatelet type	**33 (12.8)**
if surgical treatment is indicated	**31 (12.0)**
if surgical or endovascular treatment is indicated	**7 (2.7)**
if ICH or IVH is present	**4 (1.6)**
if surgical treatment and ICH or IVH is present	**7 (2.7)**
Thrombocyte transfusion	
Never	75 (29.1)
Always	11 (4.3)
individualized decision	**172 (66.6)**
depends on antiplatelet type	**31 (12.0)**
depends on aggregation test	**51 (19.8)**
if surgical treatment is indicated	**66 (25.6)**
if surgical or endovascular treatment is indicated	**11 (4.3)**
if ICH or IVH is present	**5 (1.9)**
if surgical treatment and ICH or IVH is present	**8 (3.1)**
Amount of thrombocyte transfusion	
6 units	51 (19.8)
12 or more units	13 (5.0)
depends on type of antiplatelet agent	95 (36.8)
not applicable	99 (38.4)
Physician who decides to give thrombocyte transfusion	
Neurosurgeon	66 (25.6)
(neuro)intensivist	23 (8.9)
Anaesthesiologist	13 (5.0)
after interdisciplinary discussion	108 (41.9)
not applicable	48 (18.6)
ICH: intracerebral hemorrhage, IVH: intraventricular hemorrhage	

Table 3. Crosstab of stop of antiplatelet agents and thrombocyte transfusion data in comparison to in-hospital guideline

Stop of antiplatelet agents			
	never	always	individualized decision
Guideline			
Yes	1 (1%)	50 (60%)	32 (39%)
No	8 (5%)	117(67%)	50 (29%)
Thrombocyte transfusion			
	never	always	individualized decision
Guideline			
Yes	14 (17%)	3 (4%)	66 (79%)
No	61 (35%)	8 (3.5%)	106 (61%)



1. **In which country do you work?**
   .....

2. **In which specialty do you work?**
   a) Neurosurgery
   b) Neurology
   c) General critical care
   d) Neurocritical Care
   e) Neuroradiology
   f) Medical research
   g) Other

3. **How many patients with aneurysmal subarachnoid hemorrhage (aSAH) do you treat at your hospital yearly?**
   a) < 25
   b) 25-50
   c) 50-100
   d) > 100

4. **Which department is responsible for the emergency treatment of aSAH patients in your hospital (before the aneurysm has been secured)?**
   a) Neurosurgery
   b) Neurology
   c) Intensive care
   d) Neuroradiology
   e) Emergency Department
   f) Anesthesiology

5. **Does your department have a guideline for treating patients with aSAH who have been using antiplatelet agents before onset of hemorrhage?**
   a) Yes
   b) No

6. **Do you stop the administration of antiplatelet agents in aSAH patients?**
   a) Never
   b) Always
   c) Depends on the type of antiplatelet agent(s)

      Only:
   d) If surgical treatment is indicated (e.g. EVD/ICP monitoring, aneurysm clipping)
   e) If surgical or endovascular treatment is indicated (e.g. EVD/ICP monitoring, aneurysm clipping, coiling)
   f) If intracerebral hemorrhage and/or intraventricular hemorrhage is present

7. **Do you transfuse thrombocytes when an aSAH patient has been using antiplatelet agents before onset of hemorrhage?**
   a) Never
   b) Always
   c) Depends on the type of antiplatelet agent(s)
   d) Depends on results from thrombocyte aggregation test

      Only:
   e) If surgical treatment is indicated (e.g. EVD/ICP monitoring, aneurysm clipping)
   f) If surgical or endovascular treatment is indicated (e.g. EVD/ICP monitoring, aneurysm clipping, coiling)
   g) If intracerebral hemorrhage and/or intraventricular hemorrhage is present

8. **If so, how many thrombocyte transfusions do you give?**
   a) Six units
   b) Twelve units or more
   c) Depends on the type of antiplatelet agent(s)
   d) Not applicable

9. **Do you have a cut-off in WFNS-score when giving thrombocyte transfusion?**
   a) Yes
   b) No
   c) Not applicable

10. **If yes: at which WFNS-value do you give thrombocyte transfusions?**
    a) 2
    b) 3
    c) 4
    d) 5
    e) Not applicable

11. **Who decides to give thrombocyte transfusion in case of aSAH patients who have been using antiplatelet agents?**
    a) Neurosurgeons
    b) (Neuro)intensivists
    c) Anesthesiologists
    d) The decision is made interdisciplinary
    e) Not applicable

Highlights

- Significant variability in management of aSAH patients who use antiplatelet agents.
- Stopping antiplatelet agents and/or thrombocyte transfusion is an issue of debate.
- Studies show conflicting results and optimal management is unclear.
- The presence of an in-hospital guideline appears to influence the decision.

Abbreviation list

aSAH – aneurysmal subarachnoid hemorrhage

DCI – delayed cerebral ischemia

EANS – European Association of Neurosurgical Societies

ICH – intracerebral hemorrhage